Remarks

Application Formalities

The Examiner notes that the present application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract of the present application is provided by the Applicant on a separate sheet. Therefore, this Application formality has been overcome.

Claim Objections

The Examiner points out that claim 13 depends on claim 1, which has been cancelled; therefore the Examiner requires an appropriate correction. The dependency of claim 13 has been changed from claim 1 to claim 9. Thus, it follows that this claim objection has been overcome.

Claim Rejections - 35 USC § 112

Claims 9-13 are rejected under 35 U.S.C. 112, first paragraph, because the Examiner is of the opinion that the specification does not reasonably provide enablement for *preventing*. The Examiner notes that in the absence of a definition in the specification that prophylaxis is not prevention, the term *"prophylaxis"* is interpreted as reading on *prevention*. Moreover, the Examiner considers that the instant specification fails to provide information that would allow the skilled artisan to fully practice the instant invention without undue experimentation.

Claim 9 has been amended so as to delete th term *prophylaxis*. Therefore this rejection under 35 U.S.C § 112 has been overcome.

Double Patenting

The Examiner rejects claims 9-10 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No. 5,670,534. In fact, the Examiner considers that claims 9-10 of the present specification and claims 1-7 of U.S. Patent No. 5,670,534 are not patentably distinct from each other because both sets of claims recite the treatment of endoparasitosis in an animal by administering a compound of formula I. Claim 9 has been amended so as to refer to the compound of formula I *in association or combination with a cyclodextrin*. Thus, it follows that amended claims 9-10 are patentably distinct from claims 1-7 of U.S. Patent No. 5,670,534, and that this double patenting rejection has been overcome.

Claim Rejections - 35 USC § 102

The Examiner rejects claims 9-10 and 12 as being anticipated by Animati et al. (US Patent 5,670,534, of record). Animati et al. teach a method of treating diseases caused by parasites, for example, plasmodia, in humans by administering the antiparasitic agent of formula I, where n is an integer from 1 to 4, R is NR_3R_4, R_3 and R_4 is H, A is -CONH-Z, Z is ethylene, and R_1 is -C(=NH)-NH_2. This document also teaches oral administration in an amount 0.1 to 100 mg, 1 to 4 times per day. Claims 10 ans 12 are dependent on claim 9. Claim 9 has been redrafted so as to claim a method including administration of the compound of formula I *in association or combination with a cyclodextrin*. Animati et al. does not teach the antiparasitic agent of formula I, in association or combination with a cyclodextrin (CD). Therefore amended claims 9-10 and 12 are novel over US Patent 5,670,534 and this rejection has been overcome.

Claim Rejections - 35 USC § 103

The Examiner rejects claims 11 and 13 under 35 U.S.C 103(a) as being obvious over Animati et al. (US Patent 5,670,534, of record) as applied to claims 9-10 and 12 in view of Applicant's admission of the prior art. As already discussed above, Animati et al. teach the antiprotozoarian activity of the chemical class of the inventive compounds is of formula I where n is an integer from 1 to 4, R is NR_3R_4, R_3 and R_4 is H, A is -CONH-Z, Z is ethylene, and R_1 is -C(=NH)-NH_2.

Claims 11 and 13 depend on claim 9. Claim 9 has been amended to refer to a compound of formula I in association or combination with CD.

Applicant has found that the results obtained when a compound of formula I as defined in the claims is administered in combination with CD are improved with regard to the results obtained when such compound is administered alone. An Example is herewith enclosed as ANNEX I, showing such improved results.

It shall be noted that, while the antiprotozoarian activity of the class of compounds defined in the claim may have been known, the synergistic formulation with a CD and the use of such compounds in association or combination with CD for the tretment of endoparasites in mammals is neither disclosed not suggested by the cited document.

With the aim to find a possible explanation for the aforementioned surprising and unexpected improvements in the vivo activity of the inventive compound against gastro-intestinal parasites,

Applicant tentatively resorted to the teachings of US 5,712,260. In fact, this document discloses that an appropriate CD can avoid the reprecipitation of a free drug or of a salt of the drug in physiological conditions, offering a big advantage in the administration of the drug when given in combination, rendering its bioavailability independent from any chemical and/or physiological condition found in the gastrointestinal tract of the recipient. However, Applicant does not wish to be bound to this theory or to any others. Differently from the drugs mentioned in US 5,712,260, the compounds of the present specification are not (and should not be) adsorbed by the patient (host) to exert their anti parasitic activity. Possible other explanations for the observed synergistic effect of CD in combination with the inventive compound might be likely ascribed to the intervening of some sort of (bio)physical and/or (bio)chemical interactions between CD and the parasite's cell membrane (surface) and/or biofilm, which favour the uptake of the inventive active principle by the pathogen.

It is accordingly submitted that the subject-matter of claims 9-13 fullfils the inventive step requirements and the objection under 35 U.S.C 103(a) has been overcome.

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Reconsideration of the application as hereby amended is respectfully requested.

Favorable action is respectfully solicited.

While it is believed that the amended claims properly and clearly define the present invention, applicant would be open to any suggestion or amendment the Examiner may have or propose concerning different claim phraseology which, in the Examiner's opinion, more accurately defines the present invention.

Respectfully submitted,

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ANNEX 1

EXAMPLE

The in vivo oral antiparasitic activity of the compound of formula I (R= $-CONH_2$, A= $-CONHCH_2CH_2-$; R1= $-C(=NH)-NH_2$; n= 3) in combination with a cyclodextrin was assessed by evaluating the ability of the combination to modify the course of experimentally induced infection in immuno-suppressed BALB/C mice in comparison with the inventive compound alone (Example 2). Following the same procedures as in Example 2, two groups of infected mice were treated with hydrocloride of the inventive compound plus beta-cyclodextrin (b-CD) dissolved in drinking water at a concentration of 5 µg/mL and 20 µg/mL, respectively (mice are expected to drink about 2-5 mL of water per day). The shedding of oocysts was monitored as indicated above. Compared to the experiment of Example 2, animals receiving the combined treatment showed a shorter time in the reduction in oocyst shedding (significantly observed even after only 2 days from beginning of the combination treatment) and oocysts could not be detected after 1 week of treatement with the test compound plus beta-cyclodextrin combination.